REMARKS/ARGUMENTS

Reconsideration of the Rejections and Objections of the Office Action and allowance of the claims are respectfully requested in view of Applicants' remarks below. Applicants respectfully traverse each of said Rejections and Objections. The remarks below adhere to the order the issues are presented in the Office Action.

Remarks Regarding Amendment to the Specification

The Specification has been amended to incorporate section titles and to include a Brief Description of the Drawings. The Brief Description of the Drawings merely incorporates the text which is already present in the Drawings of the Application as originally filed. The old Abstract is replaced with a new Abstract. The text of the new Abstract is supported by the claims as originally filed. The text of the old Abstract has been inserted into the Specification. Other changes to the Specification are corrections of format and typographical errors to improve readability.

No new matter is added and the entry of these amendments is respectfully requested.

Remarks Regarding Amendment to the Claims

Claims 1-10 and 13-20 are amended to conform to more clearly define the invention. The amendments are supported throughout the Specification and by the claims as original filed.

No new matter is added and the entry of the amendments is requested.

Restriction Requirement

Applicants note that claims 1-19 and 25 are examined and the species biomarkers is elected. Each of claims 1-19 and 25 read on the elected species.

Remarks Regarding Section 103

A claimed invention is unpatentable if the differences between it and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art. *In re Kahn*, 78 USPQ2d 1329, 1334 (Fed. Cir. 2006) citing *Graham v. John Deere*, 148 USPQ 459 (1966). The *Graham* analysis needs to be made explicitly. *KSR v. Teleflex*, 82 USPQ2d 1385, 1396 (2007). It requires findings of fact and a rational basis for combining the prior art disclo-sures to produce the claimed invention. See id. ("Often, it will be necessary for a court to look to interrelated teachings of multiple patents . . . and the background knowledge possessed by a person having ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue"). The use of hindsight reasoning is impermissible. See id. at 1397 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning"). Thus, a prima facie case under Section 103(a) requires "some rationale, articulation, or reasoned basis to explain why the conclusion of obviousness is correct." *Kahn* at 1335; see *KSR* at 1396.

Claims 1-24, and 26 stand rejected under 35 U.S.C. § 103(a) over each of Huyn (U.S. Publication No. 2002/0095260), Borisy (U.S. Publication No. 2003/0096309), Afeyan (U.S. Publication No. 2005/0283320), Khwaja (U.S. Patent No. 6,379,714) and Pugh (J. Argicultural Food Chem. entitled "Characterization of Aloeride, A new High MW Polysaccharide form Aloe

vera with Potent Immunostimulatory Activity"). Applicants traverse and also note that claims 20-24 and 26 are withdrawn by the Examiner in this Office Action.

In order to deal with the Examiner's rejection in respect of the prior art, it seems appropriate to first discuss the present invention and the prior art in some detail in order to illustrate the essential differences and inventive merits of the present invention when compared to the prior art.

The problem

In the last century and up to now, a western scientific approach to the discovery of new drugs from natural products has been based on the developments of methods to isolate and study molecules, evaluating the bioactivity based on a reductionistic way, *i.e.* studying the performance in target or cell-based assays.

The conventional strategy for the discovery of candidate compounds, obtained via synthesis or isolation from natural resources, designed to interact with a specific molecular target, is to seek ever-more selective compounds for the target by differential *in vitro* screening of molecules in an array of available 'target-based' assays. For this purpose large drug libraries are developed and used.

This so-called target-centric drug discovery approach is as such very time-consuming and costly. Moreover, many very specific drugs that have been identified using this approach are doomed to failure because of unanticipated effects on 'off-target' biochemical mechanisms and the safety implications of those unwanted, and sometimes fatal, side-effects might not be

revealed until a drug candidate is in large-scale clinical trials or even on the market. This is due to the fact that these specific drugs are directed towards a particular target that is only a part of the entire pathophysiology of the disease concerned and simply produce improvements in a limited number of symptoms.

Although some very successful medicines have been developed in the last 30 years, there is an increasing concern that the target-centric approach is "hitting the wall". In this respect reference is made to the fact that there is a general decline of new drug approvals each year in the United States whereas at the same time and in contrast the expenditures on pharmaceutical Research & Development have gone up considerably. Actually, these expenditures nearly doubled during the last 10 years. It is therefore not without reason that in the business environment the investment in pharmaceutical companies and related Research & Development is followed with increasing concern. Evidently, and as can be read on a regular basis in the newspapers, the decline of new drug approvals is forcing the various drug manufactures to merge with or acquire other drug manufactures.

It will be clear from the above that the nature of this target-centric drug discovery approach based on single components forms the basis of a huge problem, impacting the timely launch of new successful drugs.

The solution provided by the claimed invention

The aim of the present invention is to provide a method that solves the above-discussed problem. Surprisingly, it has been found that this can be realized in a most effective manner when use is made of an approach that differs essentially from the target-centric drug discovery

approach. This new approach is embodied in the present invention which enables highly detailed profiling and subsequent measurements of multicomponent induced changes in biological systems (biological effects) such as *in vitro* (such as cell-cultures) and in particular *in vivo* systems (such as animal models and humans). Intervention is based on the synergetic nature of multiple components at the system level, and because up to the present invention no technology or strategy had been invented that enables the discovery of a set of synergetic components in a natural product that in concert provides regulation of a biological system towards a health status.

In the method according to the present invention, the interaction of multiple components with living biological systems can very effectively be measured, using a particular set of steps wherein technologies are applied such as biostatistics and bioinformatics. In this method, the interaction of multiple natural components with living biological systems can very effectively be measured, using a particular set of steps wherein technologies are applied such as biostatistics and bioinformatics. By means of the measurements according to the present invention, the impact of multicomponent mixtures on the biological profile of a disease can advantageously be determined. Moreover, such measurements enable the choice of effective and safe components within multicomponent mixtures, and their respective concentrations required for having an impact on the biological profile of the disease can be identified.

In other words, in the method of the invention the interaction of multiple components with living biological systems can be measured, whereas in sharp contrast in the conventional target-centric drug discovery approach the biological outcome of usually a very large number of single candidate compounds or a large number of random combinations of two candidate

compounds is measured (on the basis of a drug/chemical compound library) at a molecular or a cellular level. Hence, as will be immediately appreciated by the skilled person the present method differs essentially from the known target-centric drug recovery approach as well as the discovery of synergetic components in natural products.

It cannot be emphasized enough that the present invention provides the measurement at a systems level which is crucial for almost all multifactorial diseases, not at a molecular or cellular level whereby the focus is on a particular, usually acute symptom. In this respect it is observed that the early start of a disease is often characterized by a shift in balance between different organizational structures in a system and biochemical communication and control signals are typically found at a systems level not a single cell type level. Clearly, at increasing levels of complexity in a system new properties are evolving. This communication and control element is found among others in body fluids present in a system such as blood, cerebrospinal fluid (CSF) or reflections thereof in urine. The present invention enables the discovery of system descriptors, biomarkers describing lower and higher levels of organization and control, and uses this information to optimize multicomponent natural product mixtures to address the disregulation at different pathways and different system levels.

Hence, the method according to the present invention enables the measurement of the effects of multiple target interventions and the development of products to optimally perform such interventions by a unique approach, revealing the biological profile of the effective components. In this unique approach biological systems are studied by measuring and integrating metabolic data and other profile data, such as genetic and/or proteomic data.

As will be clear from the above, the present invention stands in sharp contrast with the conventionally target-centric drug discovery approach and traditional route of isolating components from bioactive natural products. It can only be concluded that the present invention provides a unique solution to the problem associated with the conventional target-centric drug discovery approach. The present invention constitutes a considerable and major improvement over the prior art, not only in technical terms, but also in view cost-effectiveness and the benefits for society at large.

Prior art relied upon by the Examiner for the obviousness rejection

Huyn describes a biological marker identification method, wherein a set of biological measurements for observations associated with a clinical endpoint is reduced to a set of candidate measurements, and subsequently at least two biological markers are selected from the set of candidate measurements, wherein values of each biological marker predict the clinical endpoints (*e.g.* Huyn, claim 1). The disclosure of Huyn does not have any relation to the measurement of an impact of a complex mixture on a complex disease pattern, let alone identifying the bioactive profile. At best, Huyn disclose a diagnostic approach used to fish out a minimum set of relevant biomarkers. In particular, Huyn fails to teach or render obvious a step of determining a biological profile of a disease, let alone determining the impact of a series of samples of a multicomponent mixture on the biological profile.

Borisy relates to a target-centric method for identifying drug-drug interactions and uses as basis pure components. Consequently, the method of Borisy differs totally from the present invention, and this method is limited to either synthesized or purified molecules from which only

partial synergetic information can be obtained by random screening efforts. Borisy describe a screening method for the identification of combinations of known drugs (in particular small organic molecules) that exhibit previously unknown effects even where each drug has previously exhibited little or none of these effects. To identify such combinations use is made of a conventional drug library and consequently a very large number of assay measurements at cellular levels (*e.g.* Borisy, paragraphs 57-61).

Borisy clearly do not teach or suggest a method wherein the impact of a multicomponent natural product mixture is determined on the profile of a disease within a group of living systems is combined with the determination of a profile of a multicomponent natural product mixture that displays a desired impact on the profile of the disease. At best, Borisy teach the impact of a particular combination of two drugs on a particular symptom of a disease within a sub-system of a whole organism (Borisy, paragraphs 79-81). It does not teach the impact of a multicomponent natural product mixture on the biological profile of a disease as such within a living system nor does it provide any technology that is capable of measuring such information. With the technology described by Borisy, no information can be obtained on the most important part of system control and feedback signaling, such can only be obtained via a multivariate statistical approach, which approach has not been taught or suggested by Borisy. The reason for this is that the technology of Borisy concerns a conventional target-centric drug discovery method which does simply not need such an analysis technique. It is further noted that the technology as described by Borisy does simply not have the capacity to discover bioactive components in a natural product when measuring the system impact of such complex mixtures. Hence, Borisy is silent about such capacity.

The focus of Afeyan is on a method and system for profiling a biological system utilising a hierarchical multivariate analysis of spectrometric data to generate a profile of a state of a biological system. However, Afeyan completely fail to disclose or suggest steps (b) to (d) of the method of the present invention, *i.e.* (b) determining the impact of a series of samples of the multicomponent mixture on the biological profile of the disease, in which samples the concentrations of one or more natural components or groups of natural components differ, using a multivariate analysis, (c) determining the composition of the samples of the multicomponent mixture that have shown in step (b) a desired impact on the biological profile of the disease using multivariate analysis, and (d) identifying within the compositions as described in step c) the effective natural components or groups of natural components and their respective concentrations required for having the desired impact on the biological profile of the disease using multivariate analysis.

Khwaja teaches a method for making pharmaceutical grade botanical drugs, in which an aliquot is removed from botanical material. Quantitative and biological activity fingerprints of the aliquot are obtained and compared to corresponding fingerprints which have been established for a pharmaceutical grade drug. This approach is focusing on an isolation procedure, which makes it impossible to find synergetic bioactive compounds.

Pugh describes a study on the characterisation of an immunostimulatory polysaccharide called Aloeride obtained from commercial *Aloe vera*. This document describes the isolation of the compound Aloeride from a mixture and has no relation to finding synergetic compounds related to a complex disease pattern.

In addition, it is noted that in the bottom paragraph on page 4 of the Office Action the Examiner argues that the present claims read on conventional pharmacognosy, the nature of which is such that most all drug originated in natural products which are mostly a mixture of chemicals and the desired activity was found in some fashion to be associated with a specific and single chemical which was then isolated or synthesised. However, this statement of the Examiner is absolutely wrong. Traditional pharmacognosy works via isolation steps trying to find an active compound. The present invention, on the other hand, finds bioactive compound profiles that work in synergy using a disease pattern. All other approaches use a single disease marker for a disease evaluation (reductionistic approach), whereas the present invention applies multifactorial disease patterns (systemic or holistic approach).

Therefore the claimed invention is not obvious in view of the cited references at least because the references failed to disclose or render obvious all of the limitations of the claims. Withdrawal of the Section 103 rejections is requested because the claims would not have been obvious, with respect to each of the cited references or a combination of all of the cited references, to one of ordinary skill in the art when this invention was made.

Remarks Regarding Section 112, first paragraph

Claims 1-19 and 25 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. Applicants traverse.

The disclosure in the application as filed clearly demonstrates that the applicant was in possession of the claimed invention at the time the application was filed. The Example described on pages 16-18 of the international publication describes a typical experiment of how to

implement the claimed method. In addition, reference can be made to the preferred embodiment disclosed on page 14 of the international publication.

Furthermore, the determination of a biological profile of a disease from step (a) of claim 1 is described, *e.g.* in the international publication, page 8, lines 6-23. The determination of the impact from step (b) of claim 1 is described *e.g.* in the international publication, page 8, lines 24-31. The determination of the composition of the samples of the multicomponent mixture from step (c) of claim 1 is described *e.g.* in the international publication, page 8, line 32 to page 9, line 5. The identification from step (d) of claim 1 is described *e.g.* in the international publication, page 9, lines 6-12. Multivariate analysis is described throughout the application, in particular in the international publication, page 11, line 19 to page 14, line 8.

Applicants note that the terms of the claims are clearly described. Natural products are described in the Specification as originally filed on page 9, lines 23-26; improvements are described on page 15, line 32 to page 16, line 9; multivariate analysis are described on page 13, lines 12-17; and biomarkers are described on page 6, lines 23-24 and page 8, line 23.

Further, the claims have been amended to further define the invention and to be in further compliance with the written description requirement.

Withdrawal of the written description rejection made under Section 112, first paragraph, is requested because the specification conveys to a person skilled in the art that Applicants were in possession of the claimed invention as of the filing date. Their disclosure would also teach a skilled person, who possesses general knowledge available in the art, how to make and use the claimed invention.

Remarks Regarding Section 112, second paragraph

Claims 1-19 and 25 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. Applicants traverse. The specific indefiniteness issues are as follows:

Issue 1: Claims

The claims are allegedly indefinite because of the language or because they depend on an indefinite base claim. Applicants have amended the claims so to better define the invention. With respect to the term "living systems", Applicants note that the skilled person would fully understand the meaning of this term, for instance, in view of the international publication, page 2, lines 6-9. Further, Applicants note that the claim terms are not indefinite because their meaning is discernible by a person of ordinary skill in the art. Applicants respectfully submit that the language of the pending claims, as amended, is sufficiently clear so that a person of ordinary skill in the art could interpret the metes and bounds of the claim. For at least the above reasons, the claims as amended are not indefinite.

Issue 2: Remarks Regarding Title

The Title of the Application is objected to as allegedly not descriptive. Applicants traverse. Solely to expedite prosecution, Applicants have replaced the title with a new title which is the preamble to claim 1. This new title thus directly corresponds to the claimed invention and is descriptive.

Issue 3: Remarks Regarding Abstract

The Abstract is alleged to be of improper format. Applicants traverse. Solely to expedite prosecution, Applicants have submitted a new abstract which more closely reflect the current pending claims. The text of the old Abstract has been inserted into the Specification.

Applicants request withdrawal of the Section 112, second paragraph, rejections because the pending claims, Title, and Abstract, as currently amended, are clear and definite.

Remarks Regarding second Section 112, first paragraph rejection

The Specification is rejection under 35 U.S.C. 112 first paragraph as allegedly not meeting the U.S. requirements and allegedly unclear. Applicants traverse because the current Specification is clear and not indefinite.

Applicants and note that there are only guidelines that illustrate the preferred layout of patent applications and there are no absolute requirements of any specific layout. Nevertheless, in the spirit of cooperation, Applicants have amended the Specification to more closely comply with the preferred layout of a U.S. patent application.

In view of this, Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Having fully responded to the pending Office Action, Applicants submit that the claims are in condition for allowance and earnestly solicit an early Notice to that effect. The Examiner is invited to contact the undersigned if additional information is required.

Respectfully submitted,

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